ORIGINAL RESEARCH PAPER

General Medicine

A STUDY ON THE NEUTROPHIL LYMPHOCYTE RATIO AS AN EARLY PREDICTOR OF SHORT TERM MORTALITY IN PATIENTS WITH STROKE

KEY WORDS:
Stroke, Neutrophil and Lymphocyte Ratio, Diabetes, Hypertension, Dyslipidemia

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ABSTRACT

BACKGROUND: Stroke is a major cause of death and disability in many countries. Stroke mortality is higher in Asia than in Western Europe and America. So, there is a increasing need to prevent and treat stroke at the earliest. **OBJECTIVE:** The objectives of the study is to evaluate the correlation between Neutrophil and Lymphocyte Ratio (NLR) and stroke and to study the correlation between NLR and risk factors associated with stroke. **MATERIALS and METHODS:** The present study is a hospital based single centred, observational, cross-sectional study conducted in the Department of General Medicine, Silchar Medical college & hospital, Silchar, Assam. A total of 100 patients from the IPD of the Department of Medicine, Silchar Medical College and Hospital, Silchar were included randomly for the study, after fulfillment of inclusion and exclusion criteria. **RESULTS:** Among 100 stroke patients 80 patients had ischemic stroke and 20 patients had hemorrhagic stroke. Mortality was more in Haemorragic stroke 60% compared to 10% in ischaemic stroke. Increase in NLR was associated with increase in NIHSS score and increase in MRS at the time of discharge. The mean NLR in patients who expired was 10.24± 4.67 compared to alive patients who had a mean NLR of 4.62 ± 2.2. **CONCLUSION:** It can be deduced from this study that high NLR can be regarded as an independent risk factor reflecting the neurological outcome in stroke patients. Furthermore, estimation of NLR is a cost effective, easily available prognostic marker in the evaluation of the dreaded catastrophe in the form of CVA.

INTRODUCTION

Stroke is the second leading cause of death worldwide, with 6.2 million dying from stroke in 2015, an increase of 830000 since the year 2000[1]. In India the incidence rate is 119-145/100000 population[2].

A stroke, or Cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause[1] .Thus, the definition of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of complex anatomy of brain and its vasculature.

Cerebral ischaemia is caused by a reduction in blood flow that lasts longer than several seconds. If the cessation of flow lasts for more than a few minutes, infarction or death of brain tissues results. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: this is called a transient ischemic attack (TIA). But when the blood flow cannot be quickly restored, irreversible brain damage occurs, resulting in ischemic stroke. Rupture of cerebral blood vessels, leads to leakage of blood into the brain parenchyma resulting in haemorrhagic stroke, which constitutes 15% of all stroke cases and carries higher mortality rate.

Neutrophil to lymphocyte ratio (NLR) is an inflammatory biomarker that can be used as an indicator of systemic inflammation and can be readily obtained from the complete blood count, even in peripheral hospitals. Inflammation is regarded as a set of interactions between and among immune related cells such as lymphocytes, neutrophils which in turn lead to killing of tissues and destruction which is going on in stroke. One of the inflammatory markers in stroke is NLR and also has its relationship with many diseases like, myocardial infarction, COPD, chronic renal failure, etc.

In this study the association that occurs between NLR and stroke is being found out which will help us to assess the morbidity and mortality of stroke, as NLR is easy obtainable investigation and low cost one.

AIMS AND OBJECTIVES

1. The aim of the study is to evaluate the correlation between NLR and stroke
2. To study the correlation between NLR and risk factors associated with stroke
3. To evaluate the implication of NLR in stroke as a prognostic marker
4. To follow up the patient for 30 days to know the mortality.

MATERIALS AND METHODS

STUDY SETTING: The study was conducted in the Department of General Medicine, Silchar Medical College and hospital, Silchar, Assam. It is situated in the Cachar district of the Barak Valley in the state of Assam, India and is the only tertiary centre for patients of different districts of the Barak Valley of Assam and nearby North-Eastern states like Tripura, Mizoram, Manipur, Meghalaya and Nagaland.

STUDY DESIGN: The present study is a hospital based single centred, observational, crosssectional study conducted in the Department of General Medicine, Silchar Medical college & hospital, Silchar, Assam.

STUDY PERIOD: The current study was conducted over a period of one year from 1st June 2021 to 31st May 2022.

SAMPLE SIZE: A total of 100 patients from the IPD of the Department of Medicine, Silchar Medical College and Hospital, Silchar were included randomly for the study, after fulfillment of inclusion and exclusion criteria.

ETHICAL COMMITTEE APPROVAL: The present study was approved by Ethical Committee of Silchar medical college

and hospital, Silchar.

INCLUSION CRITERIA

Age >12 years. Diagnosed cases of cerebrovascular accident by imaging i.e. NCCT BRAIN. The individuals were included irrespective of sex and socio economic status.

EXCLUSION CRITERIA

Age <12 years.
Patients with malignancy and infection.
Patients with subdural or extradural hemorrhage.
Patients with neurological deficit due to any other cause.
Patients who do not give consent for the study.
Pregnant women.
Patients with hepatic disorder, renal disorders, malignancies, acute infection, fever.
Patients with connective tissue disorders.
History of recent surgery or trauma.
Patients with CNS tumors.

METHODOLOGY:-

A prior written and informed consent was obtained before evaluating the cases. Demographic data, history and physical examination were obtained and documented using the designated protocols.

1. HISTORY: A proper and thorough history was recorded. Other important factors like smoking and alcohol intake habits were enquired about and documented.

2. PHYSICAL EXAMINATION : A detailed physical examination was performed in every patient. Blood pressures were recorded using standard techniques.

3. INVESTIGATIONS : All investigations viz., Complete blood count, serum lipid profile, random blood sugar, were done in Central Composite Laboratory attached to the hospital. ECG was done to rule out any cardiac cause of stroke.

STUDY METHODS:

100 patients who had stroke were included for the study. The patients, who got admitted in Silchar Medical College and hospital were taken for the study irrespective of time of onset of signs and symptoms of acute stroke. As soon as patient got admitted, verbal consent was obtained from patient or attendant/family member(s). Then complete relevant medical history, neurological examination, routine blood and CT scan were done and all data were recorded in a standardized proforma.

CT scan was taken to differentiate between ischemic stroke and hemorrhagic stroke. National Institute of Health Stroke Scale (NIHSS) scoring was applied at the time of admission and these patients were grouped into mild, moderate and severe.

The acute ischemic stroke patients were treated according to standard treatment protocols. None of the patients in the study group were thrombolysed. Anti-edema measures were adopted with intravenous mannitol in patients of intracerebral hemorrhage. Measures were also taken to lower the blood pressure and raised ICT in patients of ICH. Modified Rankin Scale was applied to know the functional recovery of the patient after 4 weeks when patient is on follow- up.

SCORING OF STROKE PATIENTS

a. MODIFIED RANKIN SCALE (MRS)

0 - No symptoms
1 - No significant disability, despite symptoms; able to perform all usual duties and activities.
2 - Slight disability, unable to perform all previous activities but able to look after own affairs without assistance.
3 - Moderate disability, requires some help, but able to walk wit-out assistance.
4 - Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance.
5 - Severe disability; bed ridden; incontinent and requires constant nursing care and attention.
6 – Death

b. NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

NIHSS (National Institutes of Health Stroke Scale) which uses 11 different parameters for scoring the stroke patients provides a quantitative measurement of the neurologic deficit[3]. Both short and long term outcome of stroke patients can be studied using NIHSS score. It fulfills the purpose of a data collection tool for planning better patient care and also a common language for information exchanges among healthcare providers. It is a simple, valid and reliable scale that can be used at the bedside conveniently by the physicians[3]. The ability of the observer to accurately assess the patient helps in evaluation of severity of the stroke patients[3].

SCORE	STROKE SEVERITY
0	No stroke symptoms
1-4	1-4 Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

STATISTICAL ANALYSIS

The results for each parameter for discrete data are represented in numbers, percentages and average (mean, standard deviation) are represented for continuous data which are represented in tables and figures.

1. Degrees of freedom (df) = (r-1) (c-1), where r = number of rows, c=number of columns [df = number of variations that are free to vary after certain restriction have been placed on the data].

2. The student "t" test is used to determine whether there is a statistical significance between two groups in the parameters measured and "one way anova" test was used in case of three parameters . In the above test, p value of less than 0.005 was taken as the indicator of statistical significance.

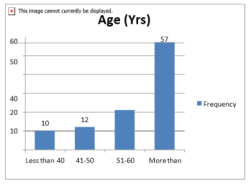
3. Chi-square (2) was used to identify the significance of the relations, associations, and interactions among various variables.

4. Pearson's correlation test was applied.

5. Statistical analysis and all the statistical graphs were prepared using Microsoft Excel and and IBM SPSS software.

RESULTS AND OBSERVATIONS

Figure 1. Graph showing age distribution of study population



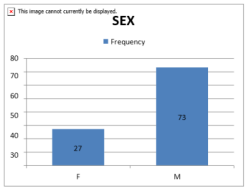


Figure 2. Graph of gender distribution in study population

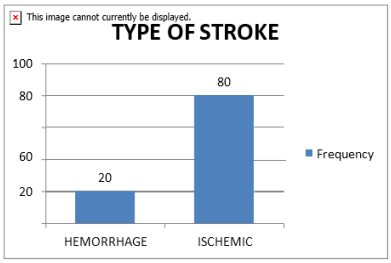


Figure 3. Graph of distribution of type of stroke according to study population

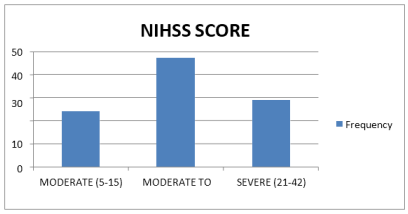


Figure 4. Graph showing distribution of study population according to NIHSS score

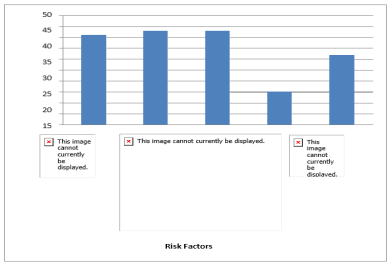


Figure 5. Distribution of study populations according to risk factors

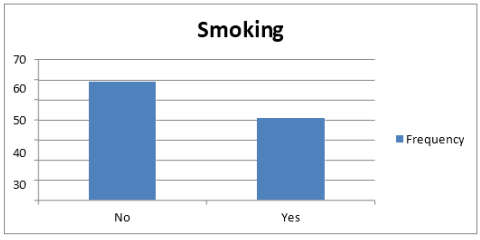


Figure 6. Distribution of study population according to smoking

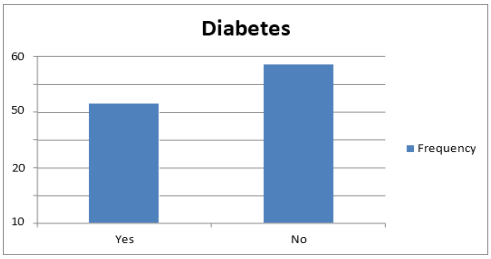


Figure 7. Distribution of study population with diabetes mellitus

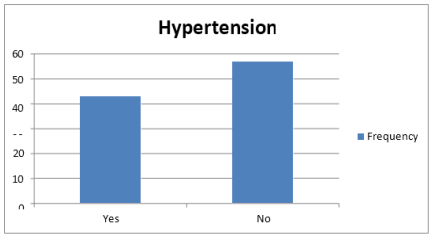


Figure 8. Distribution of study population according to hypertension

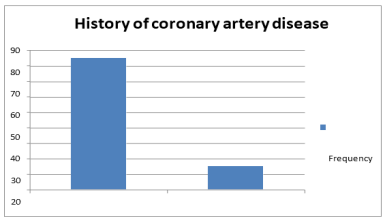


Figure 9. Distribution of study population according to history of coronary artery disease

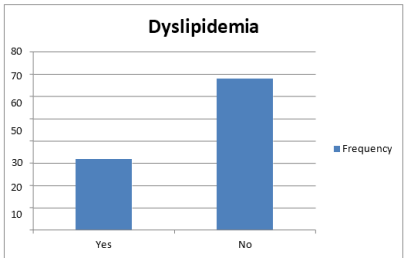


Figure 10. Distribution of study population according to dyslipidemia

Table 1. Distribution of age of study population with the type of stroke

	TYPE OF STROKE			
AGE (YRS)	HEMORRHAGE	ISCHAEMIC	TOTAL	p value
Less than 40 Years	0	10	10	0.395
41-50	3	9	12	
51-60	4	17	21	
More than 60 Years	13	44	57	
Total	20	80	100	

Table 2. Distribution of sex of study population with the type of stroke

	TYPE OF STROKE			
SEX	HEMORRHAGE	ISCHAEMIC	Total	p
Female	9	20	29	0.078
Male	11	60	71	
Total	20	80	100	

Table 3. Association of history of smoking with the type of stroke

	TYPE OF STROKE			
H/O SMOKING	HEMORRHAGE	ISCHAEMIC	Total	p value
No	12	47	59	0.919
Yes	8	33	41	
Total	20	80	100	

Table 4. Association of diabetes with the type of stroke

	TYPE OF STROKE			
DIABETES	HEMORRHAGE	ISCHAEMIC	Total	p value
No	10	47	57	0.48
Yes	10	33	43	
Total	20	80	100	

Table 5. Association of dyslipidemia with the type of stroke

	TYPE OF STROKE			
DYSLIPIDEMIA	HEMORRHAGE	ISCHAEMIC	Total	p value
No	11	57	68	0.163
Yes	9	23	32	
Total	20	80	100	

Table 6. Association of hypertension with the type of stroke

HYPERTENSION	TYPE OF STROKE			
	HEMORRHAGE	ISCHAEMIC	Total	p value
No	6	51	57	0.006
Yes	14	29	43	
Total	20	80	100	

Table 7. Relationship of age with mean NLR

	NLR			
Age (Yrs)	<5.9	>5.9	Total	p value
Less than 40 Years	7	3	10	0.195
41-50	10	2	12	
51-60	11	10	21	
More than 60 Years	30	27	57	
Total	58	42	100	

Table 8. Showing relationship of mean NLR with sex

	NLR			
SEX	<5.9	>5.9	Total	p value
Female	18	11	29	0.598
Male	40	31	71	
Total	58	42	100	

Table 9. Relationship of mean NLR with history of smoking

	NLR			
H/O SMOKING	<5.9	>5.9	Total	p value
No	38	21	59	0.119
Yes	20	21	41	
Total	58	42	100	

Table 10. Relationship of mean NLR with diabetes mellitus

	NLR			
DIABETES	<5.9	>5.9	Total	p
No	35	22	57	0.427
Yes	23	20	43	
Total	58	42	100	

Table 11. Relationship of mean NLR with dyslipidemia

	NLR			
DYSLIPIDEMIA	<5.9	>5.9	Total	p value
No	39	29	68	0.848
Yes	19	13	32	
Total	58	42	100	

Table 12. Showing relationship of mean NLR with hypertension

	NLR			
HYPERTENSION	<5.9	>5.9	Total	p value
No	38	19	57	0.043
Yes	20	23	43	
Total	58	42	100	

Table 13. Showing relationship of mean NLR with types of stroke

	NLR			
TYPE OF STROKE	<5.9	>5.9	Total	p value
HEMORRHAGE	6	14	20	0.005
ISCHEMIC	52	28	80	
Total	58	42	100	

Table 14. Relationship of mean NLR with duration of stay

NLR	N	Mean STAY (days)	SD	P value
<5.9	58	6.91	1.466	0.001
>5.9	42	8.38	2.905	
Total	100	7.53	2.294	

Table 15. Showing relationship of mean NLR with outcome

	NLR			
OUTCOME	<5.9	>5.9	Total	p value
ALIVE	54	23	77	<0.001
DEAD	4	19	23	
Total	58	42	100	

Table 16. Relationship of hypertension with NLR and TLC

HYPERTENSION		Number	Mean	SD	p value
NLR	No	57	4.978947	2.9644493	0.004
	Yes	43	7.165070	4.3930507	
	Total	100	5.918980	3.7870271	
TOTAL COUNT	No	57	6986.95	2098.484	<0.001
	Yes	43	9229.07	2900.571	
	Total	100	7951.06	2702.743	

Table 17. Relationship of outcome with NLR and TLC

OUTCOME		Number	Mean	SD	p value
NLR	Alive	77	4.626338	2.2320156	<0.001
	Dead	23	10.246522	4.6797218	
	Total	100	5.918980	3.7870271	
TOTAL COUNT	Alive	77	6930.60	1845.085	<0.001
	Dead	23	11367.39	2294.496	
	Total	100	7951.06	2702.743	

Table 18. Relationship of NIHSS score with NLR and TLC

	NIHSS SCORE	Number	Mean	SD	p value
	MODERATE	24	3.537083	1.8032567	<0.001
NLR	MODERATE SEVERE	47	4.927404	2.0269577	
	SEVERE	29	9.497241	4.6381330	
	Total	100	5.918980	3.7870271	
	MODERATE	24	6916.92	1731.860	<0.001
TOTAL COUNT	MODERATE SEVERE	47	6756.38	1868.101	
	SEVERE	29	10743.10	2498.887	
	Total	100	7951.06	2702.743	

DESCRIPTIVE STUDIES

- The minimum and maximum mean values of NLR In the study were 1.12 and 17.86 respectively, with an average mean of 5.9
- The minimum and maximum mean values for NIHSS scoring system in the study were 5 and 42 respectively, with an average mean of 21.93
- The minimum and maximum mean values for MRS scoring system in the study were 3 and 6 respectively, with an average mean of 3.98
- From this, it is evident that patients with a minimum NLR mean value of 1.12 had

a) NIHSS score minimum mean value of 5 which comes under moderate group .
b) MRS minimum mean value of 3 which comes under good outcome.
Patients with maximum NLR mean values of 17.86 had
a) NIHSS maximum mean value of 42 which comes under severe category.
b) MRS maximum mean value of 6 which comes under poor outcome.

Table 19. Relationship of mean NLR with NIHSS score

	NLR			p value
NIHSS SCORE	<5.9	>5.9	Total	
MODERATE	22	2	24	0.0003
MODERATE SEVERE	29	18	47	
SEVERE	7	22	29	
Total	58	42	100	

Table 20. Relationship of MRS with mean NLR ratio

	NLR			p value
MRS	<5.9	>5.9	Total	
Good Outcome	46	8	54	<0.001
Poor Outcome	12	34	46	
Total	58	42	100	

PEARSON CORRELATION AND SCATTER PLOT ANALYSIS

The table signifies the strong correlation between NLR and NIHSS score. Change in NLR correlates with change in NIHSS scores. There is also positive correlation between NIHSS score and NLR, that is any increase in NLR will increase NIHSS scores and decrease in NLR will decrease NIHSS score.

	Correlation Between NLR and NIHSS SCORE
Pearson Correlation	.678
p value	<0.001
N	100

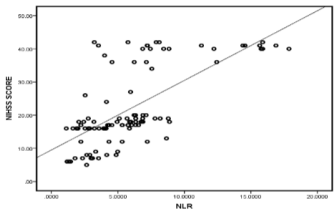


Figure 11. Scatter plot of NLR with NIHSS score

Correlation between NLR vs MRS SCORE	
Pearson Correlation	.685**
p value	<0.001
N	100

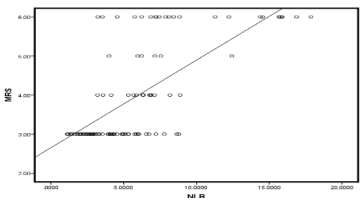


Figure 12. Scatter plot of NLR with MRS

The table signifies the strong correlation between NLR and MRS score. Change in NLR correlates with change in MRS scores. There is also positive correlation between MRS score and NLR, that is any increase in NLR will increase MRS scores and decrease in NLR will decrease MRS score.

DISCUSSION

In the present study, the age of the study population ranges from 29 to 89 years. The maximum number of subjects i.e. 57% were in the age group of more than 60 years. The mean age of the cases in our study was 61.53±14.28 years. These findings are supported by the study done by James R etal, (2017)4 which had mean age of 58.44± 14.42.

The present showed a male preponderance. Out of 100 patients, 73 were males constituting 73%. This could be because of the prevalence of smoking, hypertension, diabetes mellitus and also a proactive nature of the care of the families towards males. Similar results were found in James R et al (2017)4 which was 54%.

In our study, 43% of the population had hypertension. Other studies done by Kasundra et al (2014)5 showed different value (74%) compared to our studies which may be due to geographical difference.

Out of the study population 43% had diabetes mellitus, which is more compared to the study done by James R et al (2017)4 which had 26%.

In this study 41% of the study population had the addiction of smoking. This is higher comparable to the study done by James R et al (2017)4 which had 38%, which may be attributable to geographical and cultural differences.

The mortality percentage in our study i.e., 23% is comparable to the study done by James R et al (2017)4 which had 25%, but worse than the mortality of western studies, probably because of better health care and thrombolytic intervention available.

In our study, it was seen that hypertension had significant relation with increased NLR i.e., NLR was more in patients with hypertension compared to non hypertensives which is analogous to the study done by Jhuang, YH, Kao, TW., Peng, TC. et al(2019)6

In our study it was seen that diabetes and dyslipidemia had no significant relation with NLR, which is not similar to the studies done by N., Devamsh G. et al(2019)7 and Tok D et al (2021)[8]

In our study it was seen that Smoking had no significant relation with NLR which is comparable to other studies done by Pujani M etal (2021)9 and Dewi IAA et al(2020)[10]

The mean duration of hospital stay of patients with NLR>5.9 was 8.38±2.9 and NLR <5.9 was 6.91±1.46 which is analogous to the study done by Ahmed M et al11. In patients with haemorragic stroke , the NLR was >5.9 in 70% patients compared to 35% in ischaemic stroke which is statistically significant as p value is 0.005.

In our study it was observed that there was a significant association between NLR with severity of stroke and mortality in stroke. Among 100 stroke patients 80 patients had ischemic stroke and 20 patients had hemorrhagic stroke. Mortality was more in Haemorragic stroke 60% compared to 10% in ischaemic stroke. Increase in NLR was associated with increase in NIHSS score and increase in MRS at the time of discharge. The mean NLR in patients who expired was 10.24± 4.67 compared to alive patients who had a mean NLR of 4.62 ± 2.2, which is analogous to the study done by Radu, R.A et al(2021)12, Wirawan et al(2021)13, Xue Jie et al(2021)14 and HuY et al.(2020)15.

LIMITATIONS OF THE STUDY

The study was conducted in a single centre including small number of samples within a shorter duration of time frame and comprised of a limited geographical area, nevertheless, the present study highlighted the role of NLR in influencing the outcome in stroke patients. However, a more detailed multicentric, case-control study for a longer duration covering a relatively wider geographical area ,consisting large number of sample, and representing different ethnic groups would have been ideal to precisely establish the role of NLR in the prognostication of stroke and thereby endorsing the results of the present study.

Inflammatory process is relatively complex and we are unable to measure other inflammatory markers such as

interleukin 6, tumour necrosis factor etc in our hospital because of lack of facilities. If NLR could be correlated with these inflammatory markers the results may be better.

CONCLUSION

High NLR in stroke patients on admission were strongly associated with poorer neurological outcome. It has been indicated that high NLR values were associated with high NIHSS, which indicated the severity of the stroke, also it had a positive correlation with the MRS which indicates poor outcome in high MRS patients of stroke. Patients having high NLR values had a higher mean MRS scoring at discharge or death. Further, research on the topic can help us to use NLR as a surrogate marker for stroke severity and can help us to prognosticate the patients of stroke. The results obtained in this study are in consensus with numerous national and international studies.

So it can be deduced from this study that high NLR can be regarded as an independent risk factor reflecting the neurological outcome in stroke patients. Furthermore, estimation of NLR is a cost effective, easily available prognostic marker in the evaluation of the dreaded catastrophe in the form of CVA.

It is expected that the present study will encourage newer studies and research works related to the above subject with a much more expanded approach and for a considerable duration to further cement the role of NLR in patients suffering from stroke.

ACKNOWLEDGEMENTS: We are grateful to all participants in this study.

ETHICAL APPROVAL: Ethical approval was obtained from the Institutional Ethical Committee, Silchar Medical College and Hospital, Silchar, in its meeting held on 30th December 2020.

INFORMED CONSENT: Informed consent was obtained from all the participants included in the study.

CONFLICT OF INTEREST: There was no conflict of interest.

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